(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/26799 A1

(51) International Patent Classification[7]: B01J 19/00, B01L 3/00, C12Q 1/68

(21) International Application Number: PCT/US00/27694

(22) International Filing Date: 6 October 2000 (06.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/158,518 8 October 1999 (08.10.1999) US

(71) Applicant *(for all designated States except US)*: **BIO-INFORMATICS GROUP, INC.** [US/US]; 2000 Regency Pkwy., Suite 395, Cary, NC 27511 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **LIU, Ben, Hui** [CN/US]; 1035 Kingsway Drive, Apex, NC 27502 (US).

(74) Agents: **LYN, Kevin, R. et al.**; Alston & Bird LLP, P.O. Drawer 34009, Charlotte, NC 28234-4009 (US).

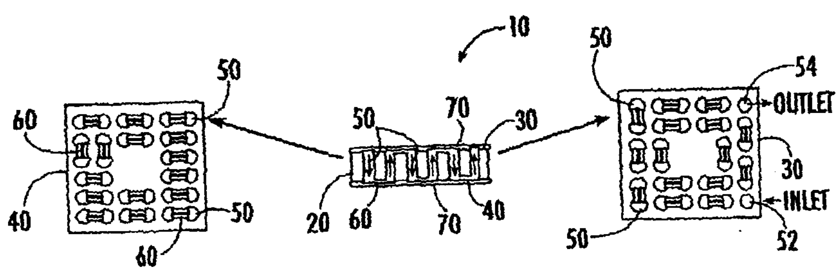
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

[Continued on next page]

(54) Title: BIOCHIP DEFINING A CHANNELED CAPILLARY ARRAY AND ASSOCIATED METHODS



WO 01/26799 A1

(57) Abstract: A biochip (10) is provided comprising a plate (20) defining a plurality of cylindrical capillaries (50), each capillary (50) having a pair of opposed ends, and a plurality of channels (60) oriented substantially perpendicularly to the capillaries (50) and configured to selectively operably connecting adjacent capillaries (50). At least one capillary (50) comprises a reagent inlet (52) and at least one capillary (50) comprises a reagent inlet (52) and at least one capillary (50) comprises a reagent outlet (54). The channels (60) operably connect adjacent capillaries (50) so as to form a continuous passage from the reagent inlet (52) to the reagent outlet (54) through each of the capillaries (50). The channels are configured such that the reagent flow is directed into a capillary (50) at one end thereof. The reagent flow is then directed from the capillary (50) at the other end thereof such that the reagent flows through substantially the length of the capillary (50). The channels (60) operably connect adjacent capillaries (50) such that the reagent is directed to flow serially through all of the capillaries (50). Several associated methods of fabricating a biochip according to the present invention are also provided, in addition to a related method of use thereof.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

BIOCHIP DEFINING A CHANNELED CAPILLARY ARRAY AND ASSOCIATED METHODS

FIELD OF THE INVENTION

The present invention relates to biological chips for conducting parallel biosample assays and, more particularly, to a biological chip defining a channeled capillary array for conducting large-scale parallel biosample assays and associated methods of use and fabrication.

BACKGROUND OF THE INVENTION

Large scale, multiple sample, parallel biochemistry assays, automated instruments, and system integration (instrument, databases and analytical tools) using the latest bioinformatics technologies are key factors for advancing the field of functional genomics. In recent years, DNA chip technology has been a focal point of genomic scientists and potential customers of genomics technology because of the ability of the DNA chip to assay a large number of genes in parallel. DNA chip technology can be used, for example, in gene expression assaying (parallel Northern blotting) to determine gene functions, in polymorphism detection and molecular marker genotyping (for example, SNP), to provide efficient genetic mapping, and, most importantly, in human disease diagnostics and in phenotype prediction for genetic manipulation of plants and animals. Further, the integration of DNA chip and two-dimensional protein data analyses is an important step in correlating the results of genomic and protemic studies.

There exist several DNA chips which are used to conduct multiple sample parallel bioassays. For example, U.S. Patent Nos. 5,800,992 and 5,744,305 to Fodor et al. discloses an oligonucleotide-based chip (herein called the "Fodor chip") and U.S. Patent No. 5,807,522 to Brown et al. discloses a cDNA-based microarray chip (herein called the "Brown chip").

The Fodor chip (U.S. Patent Nos. 5,800,992 and 5,744,305) generally utilizes a flat silicon surface for *in situ* synthesis of the oligonucleotides on the chip surface using combinatory chemistry. The Fodor chip is typically limited to short oligonucleotide lengths, where the oligos have a small number (ie: 25) of nucleotide

bases. The Fodor chip, therefore, may also be limited by experimental error associated with on-chip oligonucleotide synthesis and with short oligonucleotide hybridization error, which is generally associated with non-specific hybridization in a relaxed condition. Thus, due to these inherent experimental errors, techniques utilizing the Fodor chip may be prone to poor experimental repeatability. In addition, the Fodor chip may further be limited by slow hybridization rates due to the small effective hybridization area and random probe solution flow on the chip surface. In some instances, RNA amplification may also be required to increase the RNA concentration in the probe solution, which may make the Fodor chip unsuitable for certain applications, for example, monitoring gene expression. Thus, procedures involving the Fodor chip may be cost inefficient due to the complexities and limitations involved in producing the chip (labor intensive and time consuming), capturing the necessary images, and analyzing the collected data.

The Brown chip (U.S. Patent No. 5,807,522) utilizes cDNA samples disposed in a microarray on the surface of a chip comprising a glass slide. The cDNA segments are typically chosen from cDNA libraries of EST sequencing projects. Each cDNA segment may range in length from several hundred to several thousand nucleotides. The nucleotide sequences in the cDNA segments are generally known, though cDNA segments without nucleotide sequence information and synthetic oligos may also be used in fabricating a Brown chip. The cDNA samples are usually delivered onto the chip using a robot having a three-dimensional motion control system and the ability to concurrently deposit multiple samples using a plurality of spotting pins. However, the Brown chip may also experience limitations such as, for example, error in the x-y positioning of the spotting pins by the robot and varying amounts of the cDNA samples deposited at each spot on the chip. In addition, hybridization error may be a limiting factor due to the small effective hybridization area on the chip and possibly due to secondary structure formed by single-strand oligonucleotides. Further, techniques using the Brown chip may be subject to extended hybridization times measured, for instance, in hours (for example, overnight hybridization). As with the Fodor chip, the Brown chip may also be difficult to produce and may be limited in its practicality due to the limited surface area available on the chip.

Thus, the DNA samples reside on the surface of, for example, a glass slide or a silicon wafer according to both the Fodor and the Brown DNA chips. However, though the Fodor and Brown DNA chips are useful for some small-scale research in functional genomics, they are not suitable for future practical applications primarily due to high cost, time intensive fabrication of the DNA chip, and poor accuracy of experimental results. The poor accuracy of a surface-based biosample assay apparatus and method, for example, according to both Fodor and Brown, typically results from the low concentration of the complementary strands of DNA (or RNA) in the probe solution and the small effective hybridization area of the spots on surface-based chips. Further, the surface-based chips, such as the Brown chip, are often prepared using a robot for transferring biosamples from a mass solution to individual spots on a glass substrate to form the microarray. The biosample transfer may be accomplished, for example, by a robot operating at an overall rate of about four dots per second. Since a microarray may include, for instance, multiple thousands of individual samples, a microarray may be prone to lengthy formation times as well as possible contamination due to the robotic system.

Thus, there exists a need for a DNA chip that is cost-effective and capable of being fabricated in a more timely manner. Preferably, the DNA chip should be capable of producing more accurate and repeatable experimental results than current prior art DNA chips.

SUMMARY OF THE INVENTION

The above and other needs are met by the present invention which, in one embodiment, provides a biochip adapted to interact with a liquid reagent comprising a plate defining a plurality of cylindrical capillaries and a plurality of channels oriented substantially perpendicularly to the capillaries and configured to selectively operably connect adjacent capillaries. At least one capillary comprises a reagent inlet and at least one capillary comprises a reagent outlet. The channels operably connect adjacent capillaries so as to form a continuous passage from the reagent inlet to the reagent outlet through each of the capillaries. The channels are configured such that the reagent flow is directed into a capillary at one end thereof. The reagent flow is then directed from the capillary at the other end thereof such that the reagent flows through substantially the length of the capillary. The channels operably connect

adjacent capillaries such that the reagent is directed to flow serially through all of the capillaries.

Another advantageous aspect of the present invention comprises a method of fabricating a biochip defining a plurality of connected capillaries. First, a medial plate having a pair of opposed surfaces is formed. The medial plate defines a plurality of cylindrical capillaries, with each capillary having a pair of opposed ends. A pair of end plates is then formed, with each end plate being configured to operably engage one of the opposed surfaces of the medial plate. Each end plate further defines a series of channels configured so as to be oriented substantially perpendicularly to the capillaries. The channels are further configured to selectively connect adjacent capillaries at the ends thereof when the end plates are operably engaged with the medial plate. The end plates are then secured to the opposed surfaces of the medial plate so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary. The passage is further configured to extend substantially the length of each capillary and serially through all of the capillaries defined by the medial plate.

A further advantageous aspect of the present invention comprises a method of fabricating a biochip defining a plurality of connected capillaries. First, a mold defining a medial plate having a pair of opposed surfaces is provided. The mold further includes a plurality of cylindrical rods each having a pair of opposed ends. The rods are further operably connected by a series of connecting members oriented substantially perpendicularly to the rods about the opposed surfaces of the medial plate and selectively connecting adjacent rods at the ends thereof. A polymeric material is then introduced into the mold such that the polymer is molded into and forms the medial plate, wherein the medial plate thereby defines a plurality of capillaries corresponding to the rods and a plurality of channels corresponding to the connecting members. After the medial plate is released from the mold, the opposed surfaces of the medial plate are sealed with the corresponding end plates so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary. The passage further extends substantially the length of each capillary and serially through all of the capillaries defined by the medial plate.

A further advantageous aspect of the present invention comprises an alternate method of fabricating a biochip defining a plurality of connected capillaries. Initially, a plurality of cylindrical capillaries is etched in a medial plate having a pair of

opposed surfaces, wherein each capillary has a pair of opposed ends. A plurality of channels, oriented substantially perpendicularly to the capillaries, is then selectively etched between adjacent capillaries on each of the opposed surfaces of the medial plate. The opposed surfaces of the medial plate are then sealed with the corresponding end plates so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary. The passage further extends substantially the length of each capillary and serially through all of the capillaries defined by the medial plate.

A still further advantageous aspect of the present invention comprises a method of conducting multiple sample parallel bioassays. First, a biochip is provided, wherein the biochip defines a plurality of cylindrical capillaries having opposed ends and being selectively operably connected by a series of channels oriented substantially perpendicularly thereto and about the ends thereof so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary. The passage extends substantially the length of each capillary and serially through all of the capillaries defined by the biochip. A biosample is then immobilized on the inner walls of each of the capillaries before a liquid reagent is flowed through the passage from the reagent inlet capillary to the reagent outlet capillary, through each of the capillaries, so as to assay the biosamples.

Thus, the DNA chip according to embodiments of the present invention may be expediently fabricated in a timely and cost-effective manner. Further, the biosamples are immobilized on the walls of the capillaries. Since the biosamples adhere to the inner walls of the capillaries, the effective hybridization area is increased compared to surface-based biochips which have lower effective hybridization areas. Thus, the increased effective hybridization area facilitates detection of lower concentrations of the assayed biosample by providing a strong hybridization signal. In addition, the closed reagent flow system of the biochip according to the present invention allows the reagent probe solution flow to be more precisely controlled, thus requiring a relatively small amount of the reagent solution to provide acceptable hybridization compared to surface-based biochips. Still further, once the biochip according to the present invention is prepared with the biosamples, the biochip can be sealed and a reagent probe solution flowed in different direction and at different rates from an inlet capillary to an outlet capillary in a closed system.

The closed system and controlled flow of the reagent probe solution provides an increased hybridization rate with less false hybridization and less secondary structure disturbance as compared to surface-based biochips. Thus, the DNA chip according to the present invention is capable of providing more accurate and repeatable results due to the tighter control over critical parameters.

BRIEF DESCRIPTION OF THE DRAWINGS

Some of the advantages of the present invention having been stated, others will appear as the description proceeds, when considered in conjunction with the accompanying drawings, which are not necessarily drawn to scale, in which:

FIG. 1 is a perspective view of a biochip according to one embodiment of the present invention.

FIG. 2 is a perspective view of a capillary defined by a biochip according to one embodiment of the present invention.

FIG. 3 is a cross-sectional view of a biochip according to one embodiment of the present invention with corresponding plan views of the upper and lower surfaces of the biochip.

FIGS. 3A-1 to 3A-4 are various views of a medial plate, two opposed end plates, and a securing member comprising a biochip according to one embodiment of the present invention.

FIG. 4 is a schematic of the electrostatic fluid flow system according to one embodiment of the present invention.

FIG. 5 is a flowchart of a method of fabricating a biochip according to one embodiment of the present invention.

FIG. 6 is a flowchart of an alternate method of fabricating a biochip according to one embodiment of the present invention.

FIG. 7 is a flowchart of still another alternate method of fabricating a biochip according to one embodiment of the present invention.

FIG. 7A is a perspective view of the plate and plan views of the top and bottom surfaces thereof, with the corresponding masks for producing each portion, in accordance with one embodiment of the present invention.

FIG. 8 is a flowchart of a method of performing a multiple sample parallel bioassay in accordance with one embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention now will be described more fully hereinafter with reference to the accompanying drawings, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. Like numbers refer to like elements throughout.

FIGS. 1-3 disclose one embodiment of a biochip for conducting multiple sample, parallel bioassays, indicated generally by the numeral **10**, which includes the features of the present invention. The biochip **10** generally comprises a plate **20** having an upper surface **30** and a lower surface **40**, a plurality of capillaries **50** defined by the plate **20**, and a plurality of channels **60** selectively and operably connecting adjacent capillaries **50**.

According to one advantageous embodiment of the present invention, the plate **20** is, for instance, about one centimeter wide by one centimeter long by one-half millimeter thick. Further, the capillaries **50** have, for example, an inner diameter of about 20 microns with about 80 micron spaces between adjacent capillaries **50** such that up to 10,000 capillaries **50** may be fabricated in one biochip **10**. The capillaries **50** are generally disposed about the plate **20** in an array, though many different configurations may also be used. Accordingly, it will be understand that the dimensions and configurations of the plate **20** and the capillaries **50** may vary widely in accordance with the requirements of particular situations consistent with the spirit and scope of the present invention. For instance, the plate **20** according to one embodiment of the invention may be on the order of approximately ten centimeters wide by ten centimeters long by three millimeters thick. In addition, the capillaries **50** may vary, for example, between about 5 microns and about 1000 microns in diameter.

As shown in **FIG. 2**, the capillaries **50** further generally increase the effective hybridization surface area of the biochip **10** compared to surface-based biochips using samples comprising a spot on a flat surface. For instance, for a capillary **50** having a diameter equal to the diameter of the spot, the capillary **50** provides a hybridization surface area advantage equal to the ratio of four times the height of the capillary **50** to

the diameter of the spot. Thus, for a one-half millimeter thick plate **20** (500 microns) and a 20 micron capillary diameter, the capillary **50** provides about 100 times the hybridization surface area as compared to a 20 micron diameter spot on a surface-based biochip. A larger hybridization area provides a stronger hybridization signal, increases the hybridization rate, and tends to indicate less false hybridization. In addition, the larger hybridization area tends to reduce the likelihood of secondary structure disturbance since the chance of DNA molecules forming secondary structure is inversely proportional to the hybridization surface area. Thus, for the above example, the channeled capillary array biochip **10** would be 100 times less likely to experience DNA secondary structure disturbance than a surface-based biochip.

Where the biochip **10** includes a high density of capillaries **50**, the plate **20** is comprised of a semiconductor material such as, for example, silicon. A silicon biochip **10** uses, for instance, common semiconductor photolithography and etching processes to form the capillaries **50** in the plate **20**. More particularly, a layer of a photosensitive polymer (not shown) is deposited on a surface of the plate **20** and patterned to define a plurality of holes therein corresponding in the size and distribution to the desired capillaries **50**. The patterned layer thus comprises a mask (not shown) for forming the capillaries **50**. Once the mask is formed, the silicon plate **20** is etched through the holes in the mask to form the plurality of capillaries **50**. Production of a high density biochip **10** is facilitated by using silicon processed by semiconductor fabrication techniques since much greater precision on a smaller scale may thereby be obtained. However, where a low or medium density biochip **10** is required, the biochip **10** may be comprised of a plastic or other polymer material. Where a plastic material is used to form the biochip **10**, a mold is prepared such that the plastic may be, for instance, injection molded to form the plate **20**.

As shown in **FIGS. 1 and 3**, the capillaries **50** are generally symmetrically and evenly disposed about the plate **20** and extend from the upper surface **30** to the lower surface **40** thereof. Lateral channels **60** are further formed in the plate **20** to selectively operably connect adjacent capillaries **50** about both the upper surface **30** and the lower surface **40**. Note that the orientation-related references used herein, such as "upper," "lower," and "lateral," are used for example only in reference to the corresponding figures. It will be understood that a biochip according to embodiments of the invention may be configured in many different orientations wherein such a

reference frame may not be applicable. Preferably, the capillaries **50** are each connected to one adjacent capillary **50** on the upper surface **30** by a channel **60** and to a different capillary **50** on the lower surface 40 by another channel **60**. Most preferably, the channels **60** operably connect adjacent capillaries **50** such that a single continuous passage is formed between at least one reagent inlet capillary **52** and at least one reagent outlet capillary **54**. Thus, for a fluid or reagent probe solution flowing through the passage, the fluid would be directed along the length of the reagent inlet capillary **52**, through a channel **60** on the lower surface **40** to an adjacent capillary **50**, and then along the length of that capillary **50** before being directed through still another channel **60** on the upper surface **30** to another adjacent capillary **50**. This process continues until the fluid is directed serially through all of the capillaries **50** and along the length of the reagent outlet capillary **54**.

According to one embodiment of the present invention, as shown in **FIG. 3**, the plate **20** may be formed such that the channels **60** operably connecting adjacent capillaries **50** on both the upper surface **30** and the lower surface **40** are open with respect to the upper and lower surfaces **30** and **40**. The open upper surface **30** and lower surface **40** permit access to the capillaries **50** and facilitate immobilization of the biosample on the inner walls **56** of the capillaries **50**. Once the plate **20** has been prepared with the biosample such that the biosample is adhered to the walls **56** of the capillaries **50**, the upper surface **30** and the lower surface **40** are each sealed, for example, by a glass plate **70**. The glass plates **70** seal the upper surface **30** and the lower surface **40** of the plate **20** such that the ends of the capillaries **50** are sealed and any fluid flowing through the capillary **50** is directed into and out of the capillary **50** by the channels **60**. Accordingly, a fluid, such as the probe solution, is able to flow from the reagent inlet capillary **52** to the reagent outlet capillary **54** along a continuous passage between adjacent capillaries **50**, and serially through each capillary **50** in the plate **20**, to the reagent outlet capillary **54**. Appropriate mechanisms (not shown) are preferably provided in the glass plate **70** sealed to the upper surface **30** (or lower surface **40**) of the plate **20** to allow the flow of a reagent probe solution through the glass plate **70** into the reagent inlet capillary **52** and from the reagent outlet capillary **54**.

It will be understood, however, that a biochip **10** according to embodiments of the present invention may be fabricated in many different configurations consistent

with the spirit and scope of the present invention. For example, as shown in **FIGS. 3A-1** to **3A-4**, the biochip **10** may be fabricated so as to comprise a medial plate **25** as shown in **FIG. 3A-1**, corresponding end plates **35** and **45** as shown in **FIGS. 3A-2** and **3A-3**, respectively, and a securing member **75** as shown in **FIG. 3A-4**. In such an instance, the medial plate **25** defines a plurality of capillaries **50** that extend between the upper and lower surfaces **30** and **40** as shown in **FIG. 3A-1**.

As shown in **FIG. 3A-2**, a top end plate **35** is configured to have a surface **34** for engaging the top surface **30** of the medial plate **25**. The surface **34** further defines a series of channels **60**, each configured to extend between adjacent capillaries **50** of the medial plate **25**. At least one channel **60** comprises a reagent inlet channel **33** corresponding to the reagent inlet capillary **52** and at least one channel **60** comprises a reagent outlet channel **32** corresponding to the reagent outlet capillary **54**. As shown in **FIG. 3A-3**, a bottom end plate **45** is also configured to have a surface **44** for engaging the bottom surface **40** of the medial plate **25**. The surface **44** further defines a series of channels **60**, each also configured to extend between adjacent capillaries **50** of the medial plate **25**. Accordingly, when the top end plate **35** and the bottom end plate **45** engage the medial plate **25**, the channels **60** in the respective end plates **35** and **40** engage the corresponding capillaries **50** in the medial plate **25** so as to form a continuous passage extending serially through all of the capillaries **50**, and along the length of each, from the reagent inlet channel **32** to the reagent outlet channel **33**.

As shown in **FIG. 3A-4**, once the end plates **35** and **45** are engaged with the medial plate **25**, a securing member **75**, in one instance, a "C" shaped section, engages corresponding tracks **31** and **41** in the end plates **35** and **45**, respectively, (wherein two such securing members **75** are used in the illustrated embodiment) to maintain a sealing relation between the end plates **35** and **45** and the medial plate **25**. However, it will be further understood that the sealing relation between the end plates **35** and **45** and the medial plate **25** may be accomplished by many different forms of connecting members or other appropriate mechanisms consistent with the spirit and scope of the present invention.

According to some embodiments of the present invention, the reagent probe solution flow originates from and returns to a hybridization chamber (not shown) connected to the reagent inlet capillary **52** and the reagent outlet capillary **54**, thereby forming a closed system for a flow of the reagent. Having a closed reagent flow

system generally permits a lower quantity of the reagent solution to be used compared to surface-based biochips. For example, a maximum RNA concentration can be attained with 0.1 microliters of a reagent probe solution. In contrast, the Brown chip requires more than 10 microliters of the reagent solution to carry out the hybridization reactions using a surface-based biochip configuration.

Due to the relatively small sizes of the capillaries **50** and the channels **60** and the small amount of the reagent probe solution used during the hybridization process, precise control over the flow rate of the reagent probe solution is desirable. As shown in **FIG. 4**, "pumping" of the reagent probe solution through the capillary **50** may be accomplished using electrostatic pressure generated by a voltage applied across the two ends of a capillary **50**. Generally, high voltage of, for example, 1-20kV is required to generate the necessary pressure. By using electrostatic pressure to pump the reagent probe solution through the continuous passage formed by the capillaries **50** and the channels **60**, the voltage may be readily reversed such that the system is capable of pumping the reagent probe solution in the opposite direction. Alternating directions of the reagent probe solution flow may thereby allow a more complete and faster hybridization process compared to surface-based biochips. For example, several reversals of reagent flow may be necessary to obtain complete hybridization. The movement of molecules by the application of a plurality of electrical fields is further described in U.S. Patent No. 5,126,022 to Soane *et al.*, the contents of which are herein incorporated by reference.

According to chemical kinetics, the total number of collisions between the DNA fragments in the biosample and the complementary strand in the probe solution is a function of the hybridization area, the concentration of the complementary strand in the probe solution, and the velocity of the DNA molecules in the probe solution. Thus, control of the flow rate of the probe solution is advantageous compared to the random flow used by surface-based biochips. The use of small diameter capillaries **50** with controlled flow of the probe solution further increases effective concentration of the complementary RNA strands. In one embodiment, for example, the effective concentration of the RNA strands in the probe solution may be up to 300,000 times greater than a comparable a surface-based biochip. Thus, control of the probe solution flow and the higher effective hybridization area provides more complete hybridization, with a higher hybridization rate, and reduces the amount of the probe

solution required to perform the assay. In one embodiment, for example, the time necessary to complete a hybridization procedure may be on the order of minutes as compared to hours of hybridization time that may be required for surface-based biochips.

Another advantageous aspect of the present invention comprises a method of fabricating a biochip defining a plurality of connected capillaries, as shown in **FIG. 5**. A medial plate **25** having a pair of opposed surfaces **30** and **40** is first formed (**block 100**). The medial plate **25** generally defines a plurality of cylindrical capillaries **50** with each capillary having a pair of opposed ends. A pair of end plates **35** and **45** is then formed (**block 105**), wherein each end plate **35** and **45** is configured to operably engage one of the opposed surfaces **30** and **40** of the medial plate **25**. Each end plate **35** and **45** further defines a series of channels **60** configured so as to be oriented substantially perpendicularly to the capillaries **50** such that the channels selectively connect adjacent capillaries **50** at the ends thereof when the end plates **35** and **45** are engaged with the medial plate **25**. The end plates **35** and **45** are then secured to the opposed surfaces **30** and **40** of the medial plate **25** (**block 110**) so as to form a continuous passage extending substantially the length of each capillary **50** and serially through all of the capillaries **50**.

Still another advantageous aspect of the present invention comprises a method of fabricating a biochip defining a plurality of connected capillaries as shown in **FIG. 6**. A mold is first provided which defines a medial plate **25** having a pair of opposed surfaces **30** and **40** (**block 115**). The mold further includes a plurality of cylindrical rods with each rod having a pair of opposed ends. Further, the mold includes a series of connecting members oriented substantially perpendicularly to the rods about the opposed surfaces of the medial plate **25** and selectively connecting adjacent rods at the ends thereof. Once the mold is prepared, a polymeric material is introduced into the mold such that the polymer forms the medial plate **25** (**block 120**). This process of forming the medial plate **25** may be accomplished by, for example, using an injection molding process. The medial plate **25** may be comprised of, for example, polycarbonate. Once the polymer has been injected into the mold and solidifies, the mold is removed and the medial plate **25** released (**block 125**). The upper surface **30** and the lower surface **40** of the medial plate **25** are then sealed (**block 130**), for example, by corresponding end plates, such as glass plates **70**, so as to form a

continuous passage between the plurality of capillaries **50** such that the passage directs the reagent solution flow from the reagent inlet capillary **52** to the reagent outlet capillary **54**. The passage extends substantially the length of each capillary **50** and serially through all of the capillaries **50** defined by the medial plate. Note, however, that the mold may be configured such that the medial plate **25** defines the capillaries **50** while the end plates **35** and **45** define the connecting channels **60** as previously described in conjunction with **FIGS. 3A-1** to **3A-4**. Thus, it will be understood that a method according to the described embodiment may be altered so as to form various combinations of components which, when assembled, form a biochip **10** according to the configurations described herein. Production of the medial plate **25** and/or the end plates **35** and **45** by injection molding of a polymer is particularly advantageous where the biochip **10** includes a low to medium density of capillaries **50**, wherein a low density biochip **10** may be on the order of up to 200 capillaries per square centimeter, and a medium density biochip **10** may include up to 2,000 capillaries per square centimeter.

Still a further advantageous aspect of the present invention comprises an alternate method of fabricating a biochip defining a plurality of connected capillaries, as shown in **FIG. 7**. A plurality of cylindrical capillaries **50** is first etched in a medial plate **25** having a pair of opposed surfaces wherein the capillaries **50** each have a pair of opposed ends **(block 135)**. A plurality of channels **60** between adjacent capillaries **50** is then selectively etched on each of the upper surface **30** and the lower surface **40** of the medial plate **25** such that the channels **60** are oriented substantially perpendicularly to the capillaries **50 (block 140)**. The upper surface **30** and the lower surface **40** of the medial plate **25** are then sealed **(block 145)** with corresponding end plates so as to form a continuous passage from a reagent inlet capillary **52** to a reagent outlet capillary **54**. The passage generally extends substantially the length of each capillary **50** and serially through all of the capillaries **50** defined by the medial plate **25**. The method according to this embodiment is particularly advantageous where the biochip **10** requires a high density of capillaries **50**, wherein a high density biochip **10** includes up to 200,000 capillaries per square centimeter.

High density biochips **10** may be made of a semiconductor material such as, for instance, silicon, which thereby allows semiconductor fabrication techniques to be applied to form the capillaries **50** and channels **60**. As shown in **FIG. 7A**, a flat plate

20 comprised of silicon is coated with a light-sensitive polymer, commonly known as a photoresist. Once the photoresist coating has been applied, a mask **80** is then applied thereover and the photoresist exposed in order to pattern the photoresist and complete the photolithography process. Thus, the mask **80** can be used to define the circles **82** corresponding to the locations of the capillaries **50** in the desired configuration thereof such as, for example, an array. The patterned photoresist is then removed such that the photoresist layer remaining on the plate **20** defines a plurality of circles in the desired locations of the capillaries **50**. The plate **20** is then exposed to an etching process such that the areas within the circles defined by the photoresist are removed and the capillaries **50** formed through the thickness of the plate **20**. This process allows fine capillaries **50** with close spacing therebetween to be produced through the plate **20**, thereby providing a high density biochip **10** for accommodating a larger amount of biosamples to be assayed.

Once the capillaries **50** have been formed in the plate **20**, the photoresist layer is removed. A second photoresist layer is then applied to one of the upper surface **30** and the lower surface **40** and patterned with a mask **84** to define a plurality of lateral channels **60** connecting adjacent capillaries **50**. The plate **20** is then exposed to another etching process which produces shallow trenches in the surface of the plate **20** between the selected capillaries **50**. Following the formation of channels **60** on the first surface, the opposite surface is exposed to the same photolithography procedure using another mask **86**, followed by the etching procedure, to form the complementary channels **60** to operably connect adjacent capillaries **50** and form a continuous serial passage between all of the capillaries **50** from a reagent inlet capillary **52** to a reagent outlet capillary **54**.

Yet another advantageous aspect of the present invention comprises a method of conducting multiple sample parallel bioassays, as shown in **FIG. 8**. A biochip **10** is first provided defining an array comprising a plurality of cylindrical capillaries **50** having opposed ends and being selectively operably connected by a series of channels **60** oriented substantially perpendicularly thereto and about the ends thereof so as to form a continuous serial passage between capillaries **50** from a reagent inlet capillary **52** to a reagent outlet capillary **54** (**block 150**). A biosample is then immobilized on the inner walls **56** of the capillaries **50** (**block 155**) before a reagent solution is flowed from the reagent inlet capillary **52** to the reagent outlet capillary **54** through each of

the capillaries **50** to facilitate the hybridization reaction and to assay the biosamples **(block 160)**.

In order to collect the data, a scanner may be used to detect and capture bioassay signals. Alternatively, the bioassay signals may be detected and captured electronically through sensors and/or circuits fabricated in the biochip **10**.

Thus, a biochip according to the present invention provides a large hybridization area for conducting bioassays by using the wall of a cylindrical capillary on which to immobilize the samples. Further, high hybridization rates are obtained due to the controllability of the reagent probe solution flow and the large effective hybridization area, particularly when a high RNA concentration is used in the reagent probe solution. Accordingly, a faster and more complete hybridization process is realized. A biochip according to the present invention can thus be produced in a timely and cost-effective manner. In addition, preparation of a biochip according to the present invention, with the biosample to be assayed, is facilitated by the capillary configuration, which is less sensitive to error associated with application of the biosample to the biochip than surface-based biochips.

Many modifications and other embodiments of the invention will come to mind to one skilled in the art to which this invention pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the invention is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

THAT WHICH IS CLAIMED:

1. A biochip adapted to interact with a liquid reagent, the biochip comprising:

a plate defining a plurality of cylindrical capillaries, each capillary having a pair of opposed ends, with at least one capillary comprising a reagent inlet and at least one capillary comprising a reagent outlet;

the plate further defining a plurality of channels oriented substantially perpendicularly to the capillaries and configured to selectively operably connect adjacent capillaries so as to form a continuous passage from the reagent inlet to the reagent outlet, the channels being further configured to direct the reagent into a capillary at one end thereof and from the capillary at the other end thereof such that the reagent flows through substantially the length of the capillary and serially through all of the capillaries defined by the plate.

2. A biochip according to Claim 1 wherein the plate is substantially flat and further comprises a medial member disposed between and operably engaging opposing distal members.

3. A biochip according to Claim 2 wherein the medial member defines the capillaries and the channels.

4. A biochip according to Claim 2 wherein the medial member defines the capillaries and the distal members define the channels.

5. A biochip according to Claim 2 further comprising at least one securing member configured to secure the distal members to the medial member in sealing relation.

6. A biochip according to Claim 1 wherein the capillaries are disposed in an array.

7. A biochip according to Claim 1 wherein the capillaries are between about 5 microns and about 1000 microns in diameter.

8. A biochip according to Claim 1 wherein the capillaries are each configured to have a voltage applied across the ends thereof so as to form an electrostatic pump capable of causing the reagent to flow in a corresponding direction therebetween.

9. A biochip according to Claim 8 wherein the voltage is reversible such that the flow of the reagent is capable of being selectively reversed.

10. A biochip according to Claim 1 wherein the capillaries are each configured to have a biosample deposited on the inner wall of the capillary such that the biosample is assayed by the reagent flowing through the capillary.

11. A biochip according to Claim 1 wherein the plate is comprised of at least one of a semiconductor material and a polymeric material.

12. A biochip according to Claim 11 wherein the plate is comprised of at least one of silicon and an injection-moldable polymeric material.

13. A biochip according to Claim 11 wherein the plate is comprised of a polymeric material when the plate defines a capillary density up to about 2,000 capillaries per square centimeter.

14. A biochip according to Claim 11 wherein the plate is comprised of a semiconductor material when the plate defines a capillary density between about 2,000 capillaries per square centimeter and about 200,000 capillaries per square centimeter.

15. A method of fabricating a biochip defining a plurality of connected capillaries, said method comprising:

forming a medial plate having a pair of opposed surfaces, the medial plate defining a plurality of cylindrical capillaries with each capillary having a pair of opposed ends;

forming a pair of end plates, each end plate being configured to operably engage one of the opposed surfaces of the medial plate, each end plate defining a series of channels configured so as to be oriented substantially perpendicularly to the capillaries and to selectively connect adjacent capillaries at the ends thereof when the end plates are operably engaged with the medial plate; and

securing the end plates to the opposed surfaces of the medial plate so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary, the passage extending substantially the length of each capillary and serially through all of the capillaries defined by the medial plate.

16. A method according to Claim 15 wherein forming a medial plate further comprises forming a medial plate defining a plurality of cylindrical capillaries disposed in an array.

17. A method according to Claim 15 wherein securing the end plates to the opposed surfaces of the medial plate further comprises securing the end plates to the opposed surfaces of the medial plate with at least one securing member.

18. A method according to Claim 15 further comprising electrostatically pumping a liquid reagent in a flow direction through the capillaries by applying a corresponding voltage across the ends of each capillary.

19. A method according to Claim 18 further comprising selectively reversing the flow direction of the reagent by reversing the voltage across the ends of each capillary.

20. A method according to Claim 15 furtner comprising depositing a biosample on the inner wall of each capillary such that the biosample is capable of being assayed by a reagent flowing through the capillary.

21. A method according to Claim 15 wherein forming a medial plate further comprises forming a medial plate from a polymeric material in an injection molding process.

22. A method according to Claim 15 wherein forming a pair of end plates further comprises forming a pair of end plates from a polymeric material in an injection molding process.

23. A method of fabricating a biochip defining a plurality of connected capillaries, said method comprising:

providing a mold defining a medial plate having a pair of opposed surfaces, the mold having a plurality of cylindrical rods, each rod having a pair of opposed ends, the mold further having a series of connecting members oriented substantially perpendicularly to the rods about the opposed surfaces of the medial plate and selectively connecting adjacent rods at the ends thereof;

introducing a polymeric material into the mold so as to form the medial plate, the medial plate thereby defining a plurality of capillaries corresponding to the rods and a plurality of channels corresponding to the connecting members;

releasing the medial plate from the mold; and

sealing the opposed surfaces of the medial plate with corresponding end plates so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary, the passage extending substantially the length of each capillary and serially through all of the capillaries defined by the medial plate.

24. A method according to Claim 23 wherein providing a mold further comprises providing a mold having a plurality of cylindrical rods disposed in an array.

25. A method according to Claim 23 wherein sealing the opposed surfaces of the medial plate with corresponding end plates further comprises sealing the opposed surfaces of the medial plate with corresponding end plates and at least one securing member configured to secure the end plates to the medial plate.

26. A method according to Claim 23 further comprising electrostatically pumping a liquid reagent in a flow direction through the capillaries by applying a corresponding voltage across the ends of each capillary.

27. A method according to Claim 26 further comprising selectively reversing the flow direction of the reagent by reversing the voltage across the ends of each capillary.

28. A method according to Claim 23 further comprising depositing a biosample on the inner wall of each capillary such that the biosample is capable of being assayed by a reagent flowing through the capillary.

29. A method according to Claim 23 wherein introducing a polymeric material into the mold further comprises introducing an injection-moldable polymeric material into the mold.

30. A method according to Claim 23 wherein providing a mold further comprises providing a mold having up to about 2,000 capillaries per square centimeter to produce a medial plate having a corresponding capillary density.

31. A method according to Claim 23 further comprising forming the end plates from a polymeric material in an injection molding process prior to sealing the opposed surfaces of the medial plate.

32. A method of fabricating a biochip defining a plurality of connected capillaries, said method comprising:

etching a plurality of cylindrical capillaries in a medial plate having a pair of opposed surfaces, each capillary having a pair of opposed ends;

selectively etching a plurality of channels, oriented substantially perpendicularly to the capillaries, between adjacent capillaries on each of the opposed surfaces of the medial plate;

sealing the opposed surfaces of the medial plate with corresponding end plates so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary, the passage extending substantially the length of each capillary and serially through all of the capillaries defined by the medial plate.

33. A method according to Claim 32 wherein etching a plurality of cylindrical capillaries in a medial plate further comprises etching a plurality of cylindrical capillaries disposed in an array in a medial plate.

34. A method according to Claim 32 wherein sealing the opposed surfaces of the medial plate with corresponding end plates further comprises sealing the opposed surfaces of the medial plate with corresponding end plates and at least one securing member configured to secure the end plates to the medial plate.

35. A method according to Claim 32 further comprising electrostatically pumping a liquid reagent in a flow direction through the capillaries by applying a corresponding voltage across the ends of each capillary.

36. A method according to Claim 35 further comprising selectively reversing the flow direction of the reagent by reversing the voltage across the ends of each capillary.

37. A method according to Claim 32 further comprising depositing a biosample on the inner wall of each capillary such that the biosample is capable of being assayed by a reagent flowing through the capillary.

38. A method according to Claim 32 further comprising patterning a photoresist deposited on the medial plate so as to define portions of the medial plate to be etched, the portions corresponding to at least one of the plurality of capillaries and the plurality of channels, prior to etching the plurality of capillaries and etching the plurality of channels.

39. A method according to Claim 32 wherein etching a plurality of capillaries further comprises etching a plurality of capillaries having a capillary density of between about 2,000 capillaries per square centimeter and about 200,000 capillaries per square centimeter.

40. A method according to Claim 32 wherein etching a plurality of capillaries in a medial plate further comprises etching a plurality of capillaries in a medial plate comprised of a semiconductor material.

41. A method according to Claim 32 wherein etching a plurality of capillaries in a medial plate further comprises etching a plurality of capillaries in a medial plate comprised of a silicon.

42. A method of conducting multiple sample parallel bioassays, said method comprising:

providing a biochip defining a plurality of cylindrical capillaries having opposed ends and being selectively operably connected by a series of channels oriented substantially perpendicularly thereto and about the ends thereof so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary, the passage extending substantially the length of each capillary and serially through all of the capillaries defined by the biochip;

immobilizing a biosample on the inner walls of each of the capillaries; and

flowing a liquid reagent from the reagent inlet capillary to the reagent outlet capillary so as to assay the biosamples.

43. A method according to Claim 42 wherein flowing a liquid reagent further comprises flowing a liquid reagent by applying a voltage across the ends of each capillary so as to electrostatically pump the reagent in a corresponding flow direction through the capillaries.

44. A method according to Claim 43 flowing a liquid reagent further comprises selectively reversing the flow direction of the reagent by reversing the voltage across the ends of each capillary.

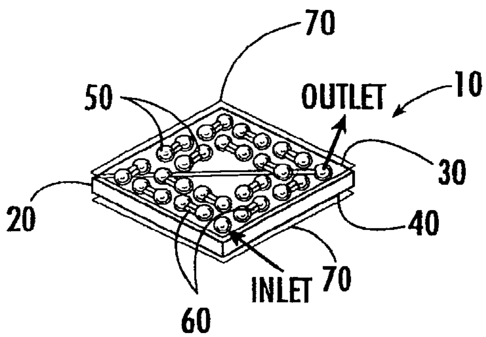


FIG. 1.

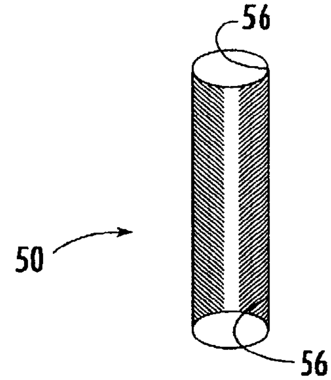


FIG. 2.

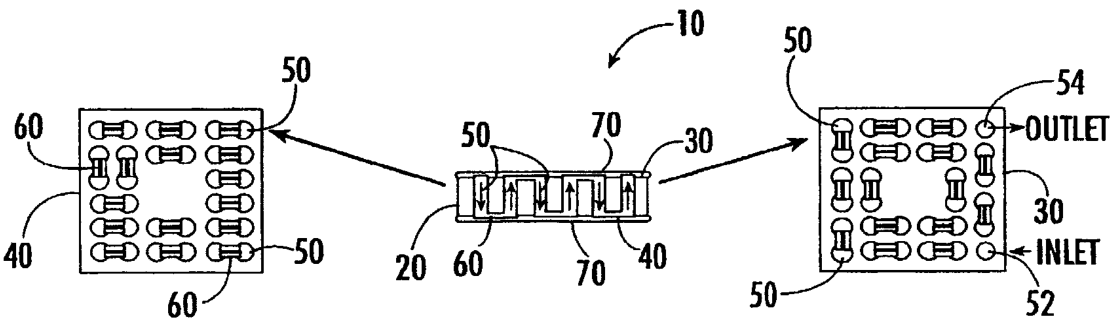


FIG. 3.

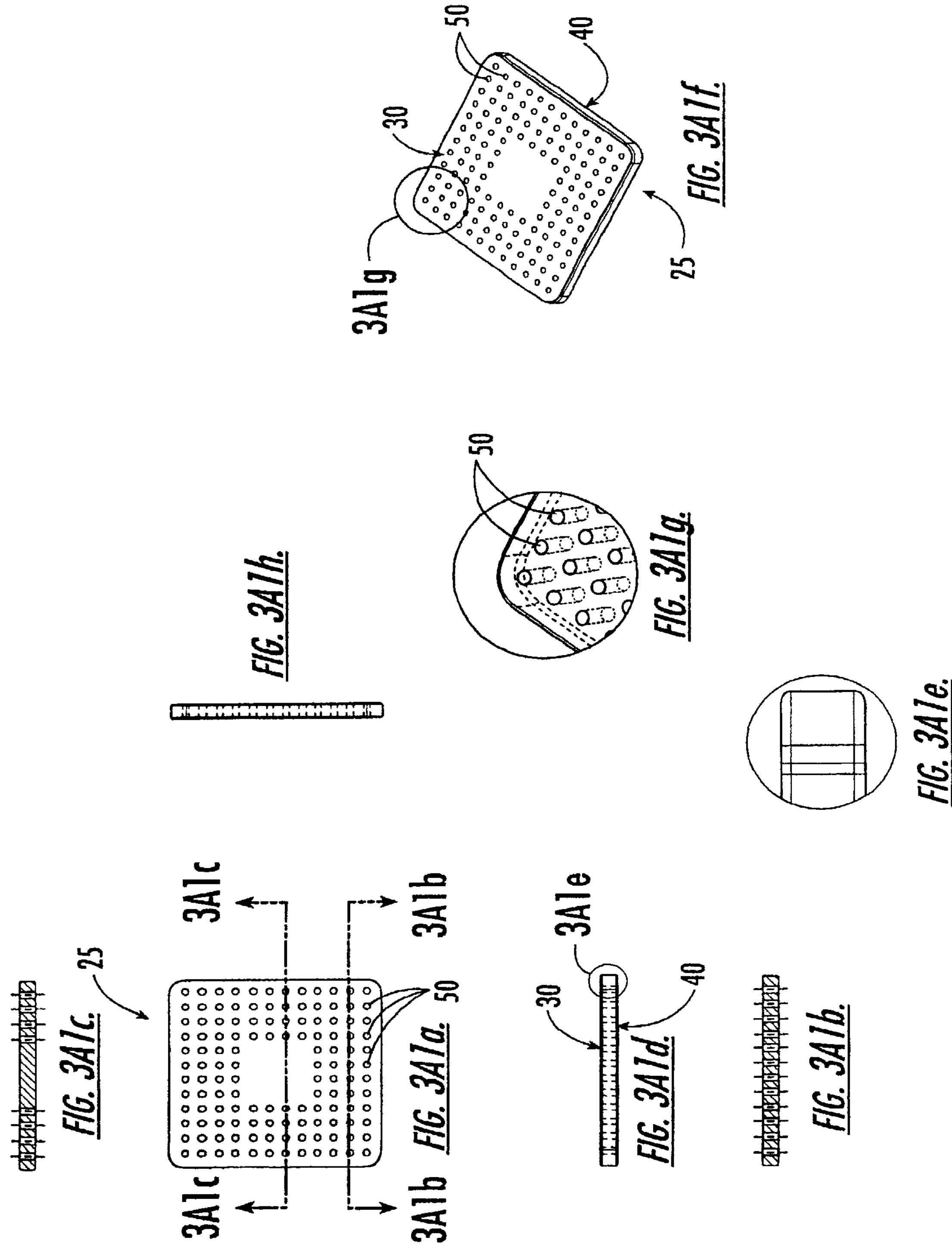


FIG. 3A1f.

FIG. 3A1g.

FIG. 3A1h.

FIG. 3A1e.

FIG. 3A1c.

FIG. 3A1a.

FIG. 3A1d.

FIG. 3A1b.

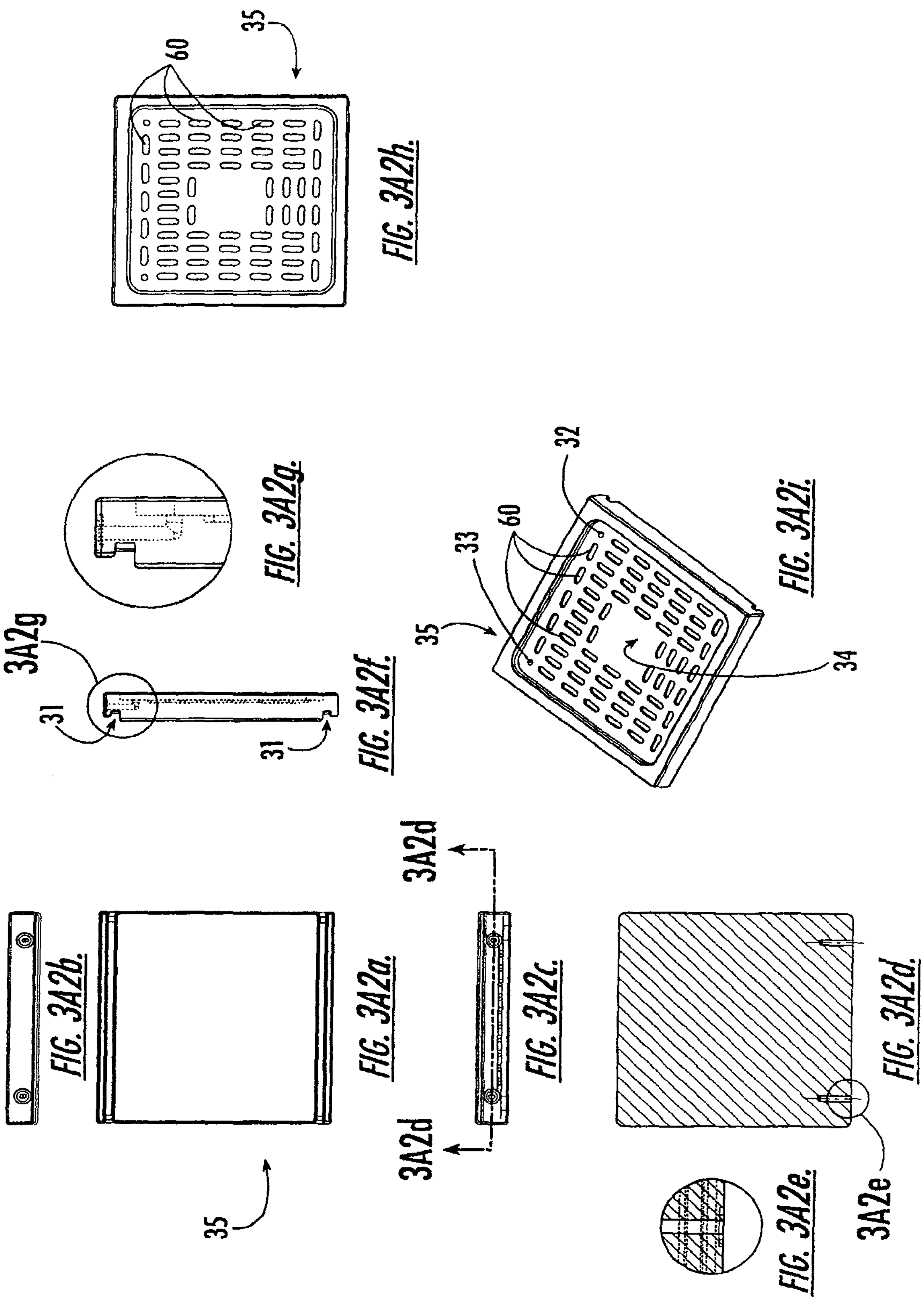


FIG. 3A2h.

FIG. 3A2g.

FIG. 3A2f.

FIG. 3A2i.

FIG. 3A2b.

FIG. 3A2a.

FIG. 3A2c.

FIG. 3A2d.

FIG. 3A2e.

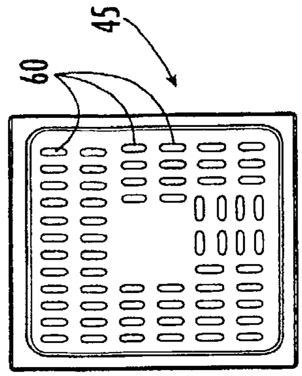


FIG. 3A3g.

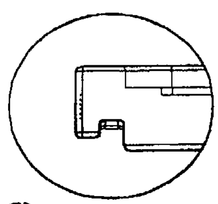


FIG. 3A3e.

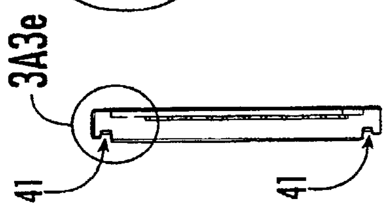


FIG. 3A3d.

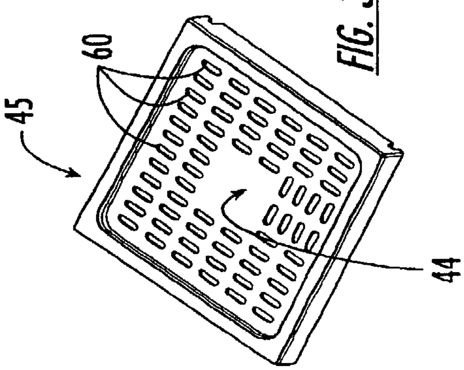


FIG. 3A3f.

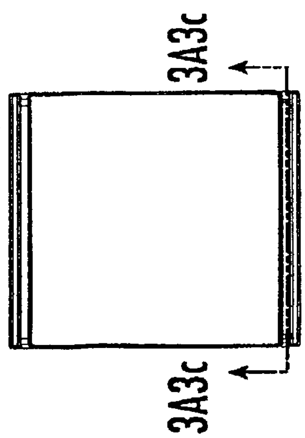


FIG. 3A3a.

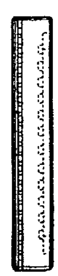


FIG. 3A3b.

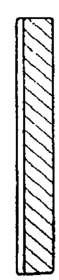


FIG. 3A3c.

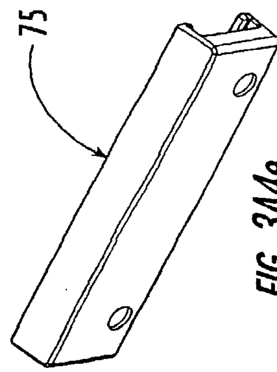


FIG. 3A4e.

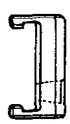


FIG. 3A4d.

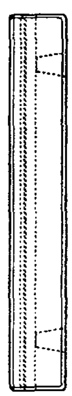


FIG. 3A4a.

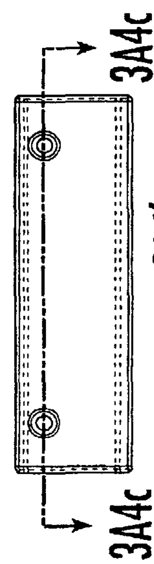


FIG. 3A4b.

FIG. 3A4c.

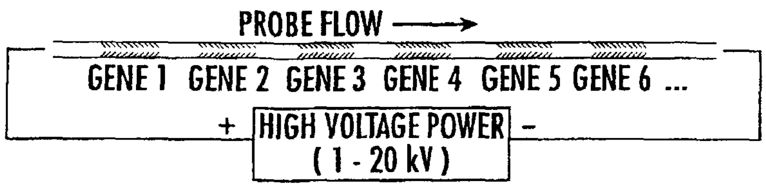

PROBE FLOW
GENE 1 GENE 2 GENE 3 GENE 4 GENE 5 GENE 6 ...
+ HIGH VOLTAGE POWER -
(1 - 20 kV)

FIG. 4.

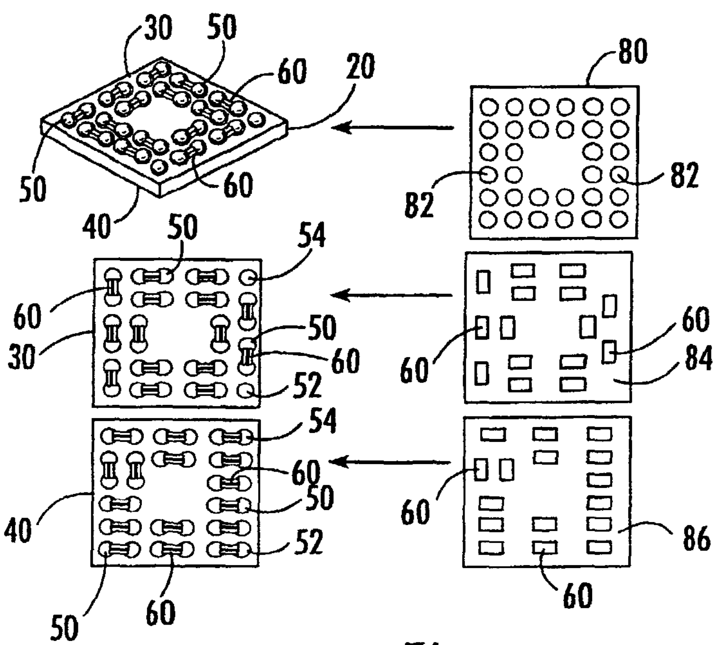

30
50
60
20
80
50
60
40
82
82
50
54
60
30
50
60
52
60
60
84
54
60
50
40
52
60
86
50
60
60

FIG. 7A.

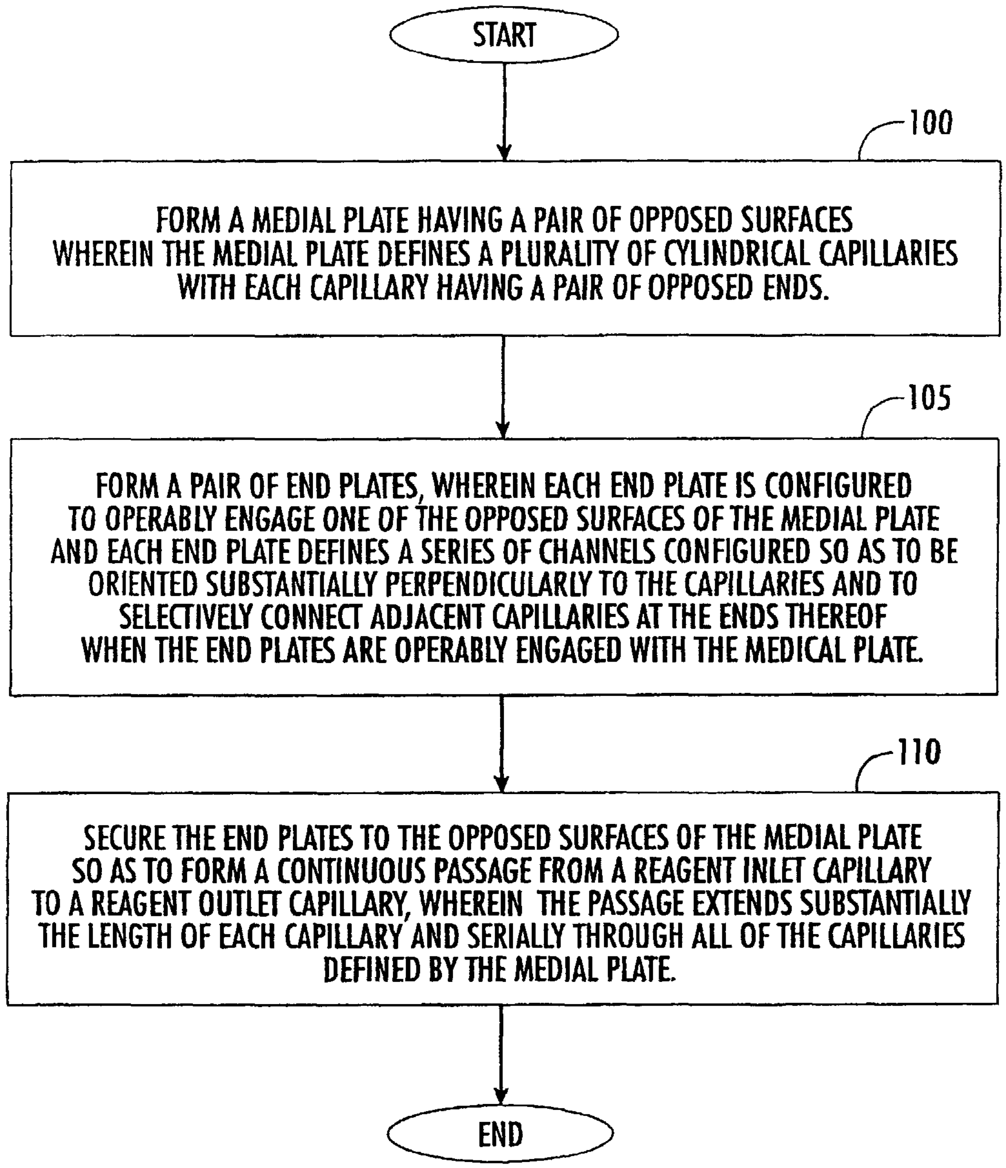

START
100
FORM A MEDIAL PLATE HAVING A PAIR OF OPPOSED SURFACES WHEREIN THE MEDIAL PLATE DEFINES A PLURALITY OF CYLINDRICAL CAPILLARIES WITH EACH CAPILLARY HAVING A PAIR OF OPPOSED ENDS.
105
FORM A PAIR OF END PLATES, WHEREIN EACH END PLATE IS CONFIGURED TO OPERABLY ENGAGE ONE OF THE OPPOSED SURFACES OF THE MEDIAL PLATE AND EACH END PLATE DEFINES A SERIES OF CHANNELS CONFIGURED SO AS TO BE ORIENTED SUBSTANTIALLY PERPENDICULARLY TO THE CAPILLARIES AND TO SELECTIVELY CONNECT ADJACENT CAPILLARIES AT THE ENDS THEREOF WHEN THE END PLATES ARE OPERABLY ENGAGED WITH THE MEDICAL PLATE.
110
SECURE THE END PLATES TO THE OPPOSED SURFACES OF THE MEDIAL PLATE SO AS TO FORM A CONTINUOUS PASSAGE FROM A REAGENT INLET CAPILLARY TO A REAGENT OUTLET CAPILLARY, WHEREIN THE PASSAGE EXTENDS SUBSTANTIALLY THE LENGTH OF EACH CAPILLARY AND SERIALLY THROUGH ALL OF THE CAPILLARIES DEFINED BY THE MEDIAL PLATE.
END

FIG. 5.

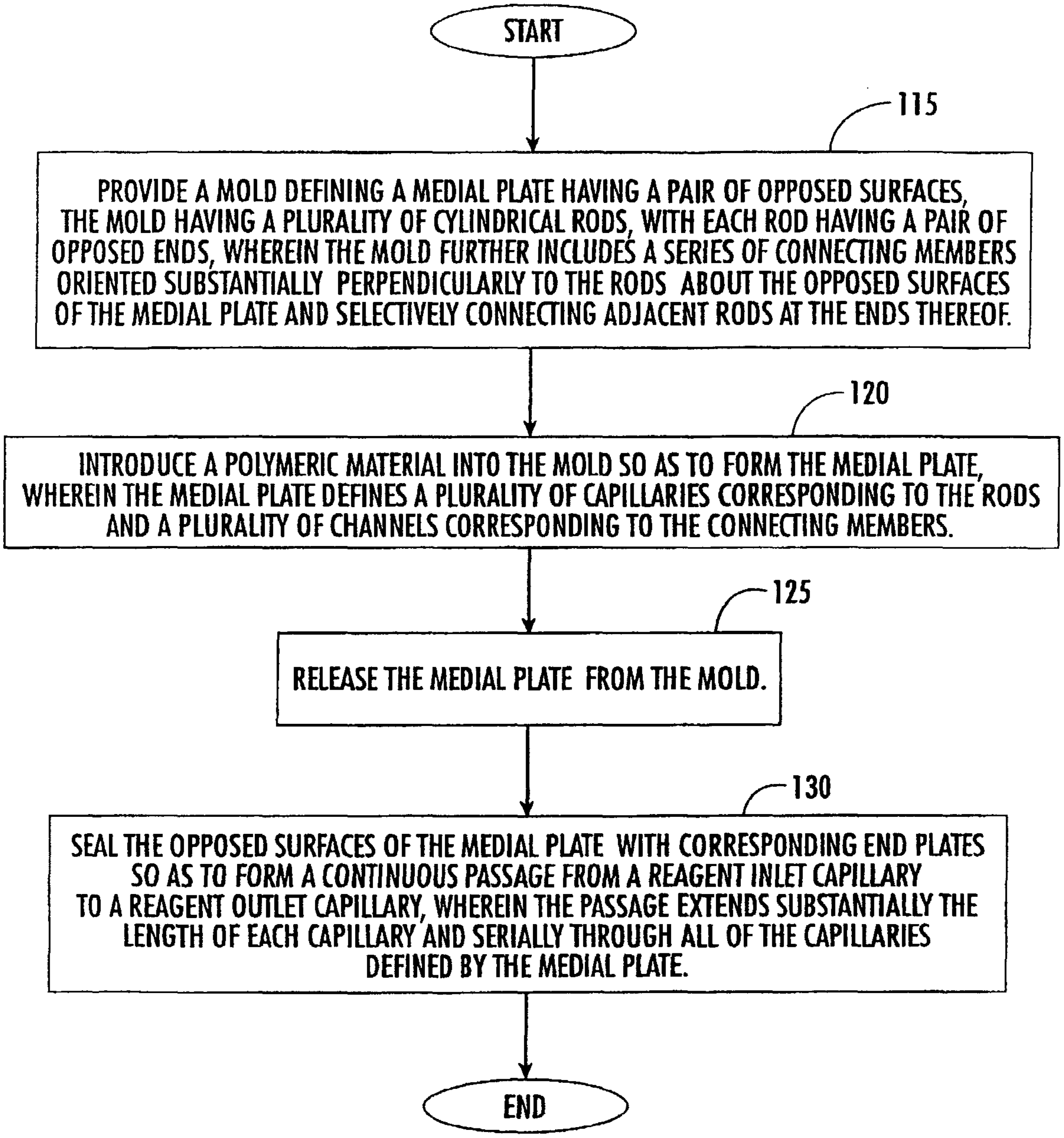

START
115
PROVIDE A MOLD DEFINING A MEDIAL PLATE HAVING A PAIR OF OPPOSED SURFACES, THE MOLD HAVING A PLURALITY OF CYLINDRICAL RODS, WITH EACH ROD HAVING A PAIR OF OPPOSED ENDS, WHEREIN THE MOLD FURTHER INCLUDES A SERIES OF CONNECTING MEMBERS ORIENTED SUBSTANTIALLY PERPENDICULARLY TO THE RODS ABOUT THE OPPOSED SURFACES OF THE MEDIAL PLATE AND SELECTIVELY CONNECTING ADJACENT RODS AT THE ENDS THEREOF.
120
INTRODUCE A POLYMERIC MATERIAL INTO THE MOLD SO AS TO FORM THE MEDIAL PLATE, WHEREIN THE MEDIAL PLATE DEFINES A PLURALITY OF CAPILLARIES CORRESPONDING TO THE RODS AND A PLURALITY OF CHANNELS CORRESPONDING TO THE CONNECTING MEMBERS.
125
RELEASE THE MEDIAL PLATE FROM THE MOLD.
130
SEAL THE OPPOSED SURFACES OF THE MEDIAL PLATE WITH CORRESPONDING END PLATES SO AS TO FORM A CONTINUOUS PASSAGE FROM A REAGENT INLET CAPILLARY TO A REAGENT OUTLET CAPILLARY, WHEREIN THE PASSAGE EXTENDS SUBSTANTIALLY THE LENGTH OF EACH CAPILLARY AND SERIALLY THROUGH ALL OF THE CAPILLARIES DEFINED BY THE MEDIAL PLATE.
END

FIG. 6.

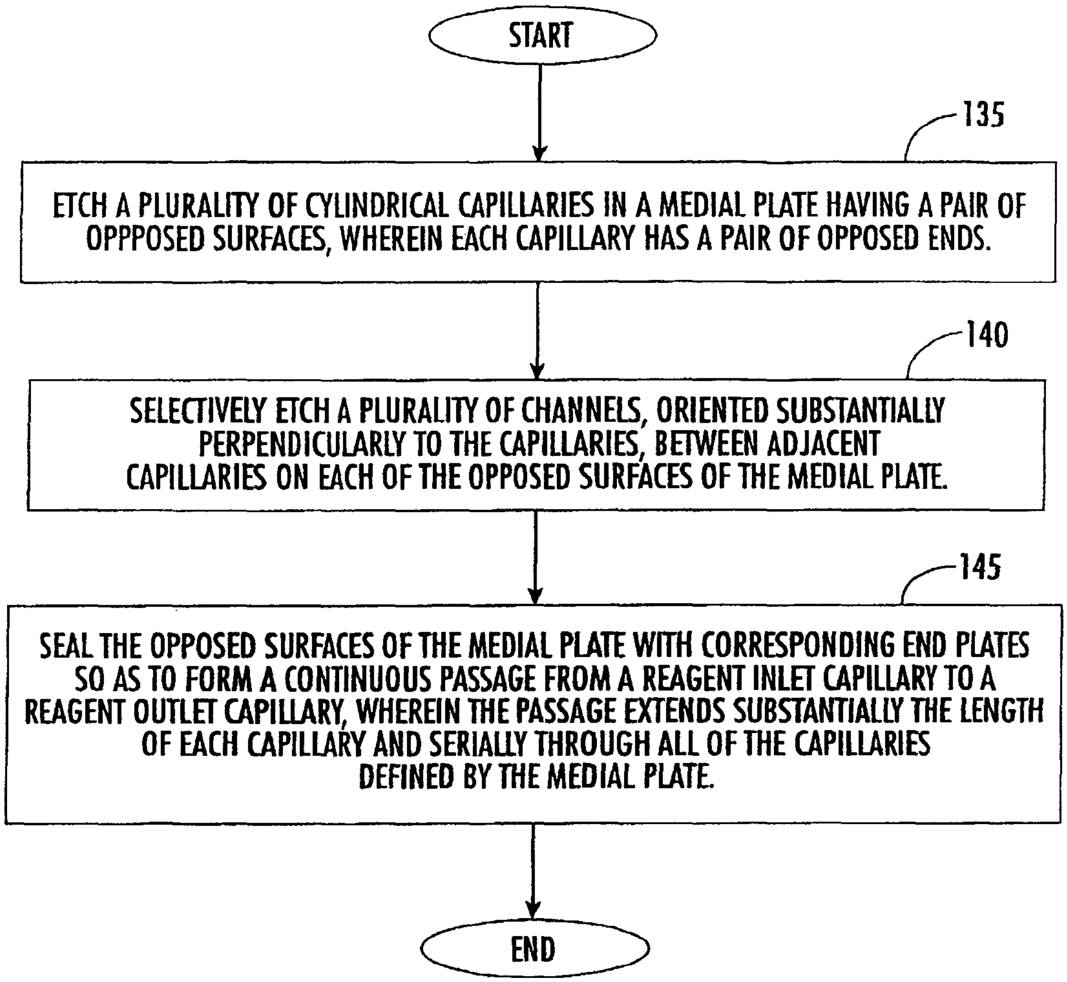

START
135
ETCH A PLURALITY OF CYLINDRICAL CAPILLARIES IN A MEDIAL PLATE HAVING A PAIR OF OPPPOSED SURFACES, WHEREIN EACH CAPILLARY HAS A PAIR OF OPPOSED ENDS.
140
SELECTIVELY ETCH A PLURALITY OF CHANNELS, ORIENTED SUBSTANTIALLY PERPENDICULARLY TO THE CAPILLARIES, BETWEEN ADJACENT CAPILLARIES ON EACH OF THE OPPOSED SURFACES OF THE MEDIAL PLATE.
145
SEAL THE OPPOSED SURFACES OF THE MEDIAL PLATE WITH CORRESPONDING END PLATES SO AS TO FORM A CONTINUOUS PASSAGE FROM A REAGENT INLET CAPILLARY TO A REAGENT OUTLET CAPILLARY, WHEREIN THE PASSAGE EXTENDS SUBSTANTIALLY THE LENGTH OF EACH CAPILLARY AND SERIALLY THROUGH ALL OF THE CAPILLARIES DEFINED BY THE MEDIAL PLATE.
END

FIG. 7.

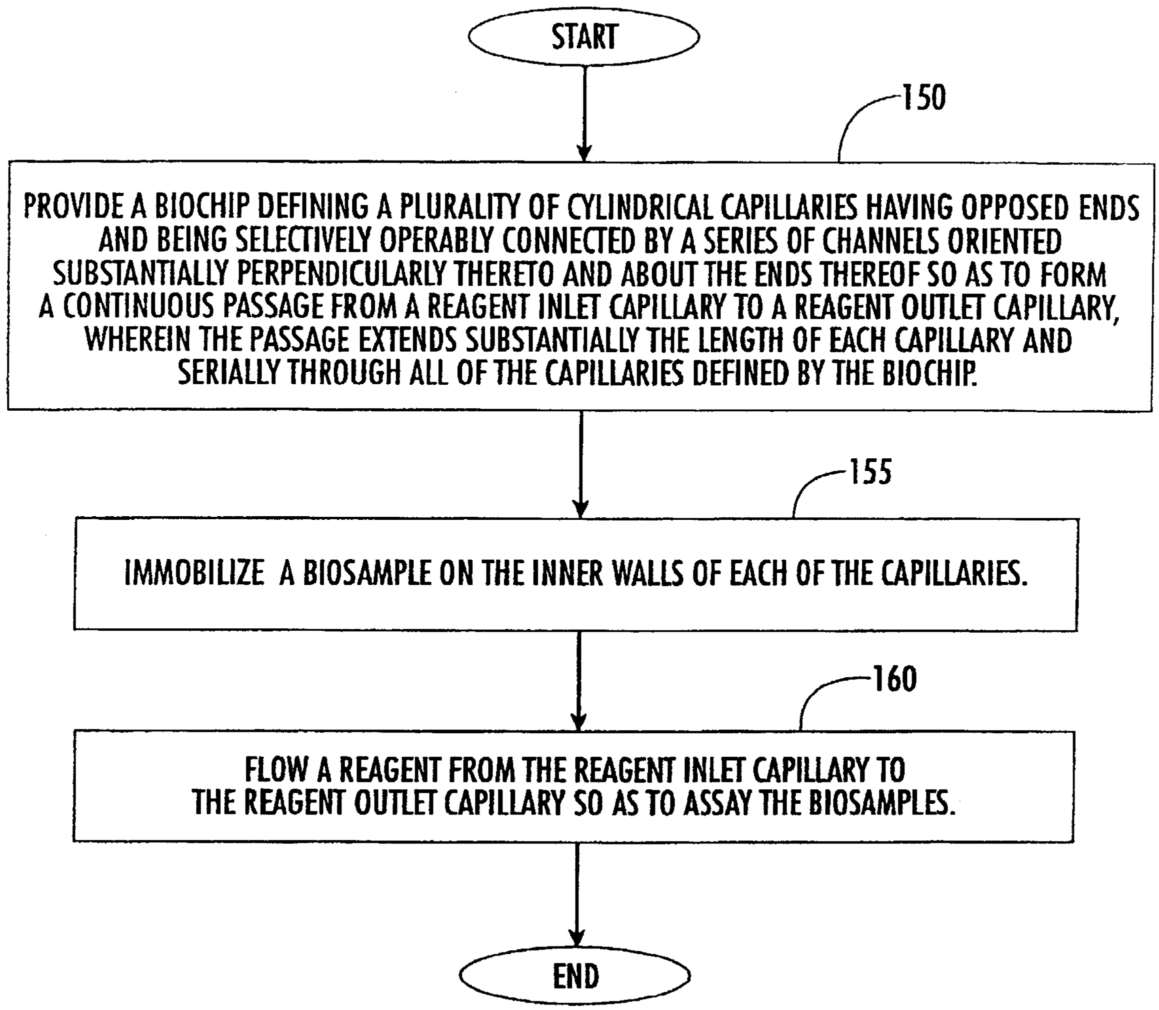

START
150
PROVIDE A BIOCHIP DEFINING A PLURALITY OF CYLINDRICAL CAPILLARIES HAVING OPPOSED ENDS AND BEING SELECTIVELY OPERABLY CONNECTED BY A SERIES OF CHANNELS ORIENTED SUBSTANTIALLY PERPENDICULARLY THERETO AND ABOUT THE ENDS THEREOF SO AS TO FORM A CONTINUOUS PASSAGE FROM A REAGENT INLET CAPILLARY TO A REAGENT OUTLET CAPILLARY, WHEREIN THE PASSAGE EXTENDS SUBSTANTIALLY THE LENGTH OF EACH CAPILLARY AND SERIALLY THROUGH ALL OF THE CAPILLARIES DEFINED BY THE BIOCHIP.
155
IMMOBILIZE A BIOSAMPLE ON THE INNER WALLS OF EACH OF THE CAPILLARIES.
160
FLOW A REAGENT FROM THE REAGENT INLET CAPILLARY TO THE REAGENT OUTLET CAPILLARY SO AS TO ASSAY THE BIOSAMPLES.
END

FIG. 8.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/27694

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J19/00 B01L3/00 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 32219 A (GLAXO GROUP LIMITED) 1 July 1999 (1999-07-01) abstract page 26, line 12 -page 27, line 10 figures 7-9	1
A	US 5 580 523 A (ALLEN J. BARD) 3 December 1996 (1996-12-03) abstract; figures	1
A	US 5 567 294 A (NORMAN J. DOVICHI & JIAN Z. ZHANG) 22 October 1996 (1996-10-22) the whole document	1
A	US 5 759 779 A (PETER J. DEHLINGER) 2 June 1998 (1998-06-02) the whole document	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search
14 February 2001

Date of mailing of the international search report
21/02/2001

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Stevnsborg, N

1

International Application No
PCT/US 00/27694

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 13313 A (GENOVATIONS, INC.) 18 March 1999 (1999-03-18) abstract page 11, line 14 - line 18 figures 7-9 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/27694

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9932219 A	01-07-1999	US 6083682 A	04-07-2000
		AU 1926499 A	12-07-1999
		EP 1069940 A	24-01-2001
US 5580523 A	03-12-1996	AU 708281 B	29-07-1999
		AU 2200195 A	23-10-1995
		CA 2186896 A	12-10-1995
		EP 0754084 A	22-01-1997
		JP 10501167 T	03-02-1998
		WO 9526796 A	12-10-1995
US 5567294 A	22-10-1996	AU 716682 B	02-03-2000
		AU 1090297 A	22-08-1997
		CA 2245167 A	07-08-1997
		WO 9728443 A	07-08-1997
		EP 0877933 A	18-11-1998
		JP 2000506606 T	30-05-2000
US 5759779 A	02-06-1998	US 5723320 A	03-03-1998
		AU 7731196 A	19-06-1997
		CA 2238303 A	05-06-1997
		EP 0876206 A	11-11-1998
		WO 9719749 A	05-06-1997
		US 5763263 A	09-06-1998
WO 9913313 A	18-03-1999	AU 7498598 A	29-03-1999
		CN 1269883 T	11-10-2000
		EP 1012564 A	28-06-2000